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# Design, synthesis and herbicidal activity study of aryl 2,6-disubstituted sulfonylureas as potent acetohydroxyacid synthase inhibitors

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## ABSTRACT

A series of sulfonylurea derivatives containing a 2,6-disubstituted aryl moiety were designed, synthesized and evaluated for their herbicidal activities. Most of these compounds showed excellent inhibitory rates against both monocotyledonous and dicotyledonous weeds, especially **10a**, **10h** and **10i**. They exhibited equivalent or superior herbicidal efficiency than commercial chlorsulfuron at the dosage of 15 g/ha and the preliminary SAR was summarized. In order to illuminate the molecular mechanism of several potent compounds, their apparent inhibition constant ($K_i^{app}$) of *Arabidopsis thaliana* acetohydroxyacid synthase (AHAS) were determined and the results confirmed that these compounds were all potent AHAS inhibitors. **10i** have a $K_i^{app}$ of 11.5 nM, which is about 4 times as potent as chlorsulfuron (52.4 nM).

Sulfonylurea herbicides are widely applied over the world owing to their ultra-low application dosage and extremely low acute toxicity to mammals. They control the growth of weeds by noncompetitively inhibiting their acetohydroxyacid synthase (AHAS, EC 2.2.1.6), the first key enzyme in branched amino acids biosynthesis pathway.[1–3] Previous studies on structure-activity relationships (SAR) have shown that the presence of a sulfonyl-*ortho* substituent is critical for the bioactivity.[4,5] Different substitution patterns on the aryl moiety could result in different species selectivity features. Our group previously found that nitro group was an excellent sulfonyl-*ortho* group with especially high security towards Millet (*Setaria italica*),[6,7] a popular crop in Northern China. At the same time, it is worth noting that there are totally two sulfonyl-*ortho* positions in the molecule, both of which could be substituted, just like the pattern of Triflusulfuron-methyl, a sugar beet herbicide.[8,9] However, there are seldom reports about the 2,6-disubstituted sulfonylureas in addition to this.[10,11] The halogens were presumed as suitable substituents considering the electrostatic and hydrophobic characters. An alkoxy group was introduced in order to fit the geometric configuration of the herbicide binding site[12,13] and enhance the hydrophobicity of the target molecule. In view of the above-mentioned basis, a series of aryl 2,6-disubstituted sulfonylureas containing a nitro group was designed and synthesized (Fig. 1), in the hope to find potent lead compounds with interesting selectivity characteristics. Biological evaluation of these compounds was carried out.

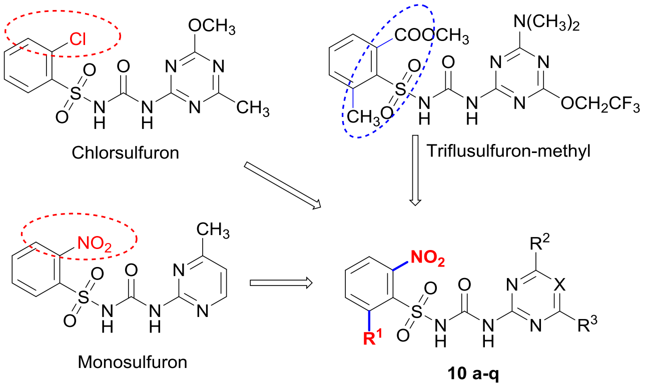

**Fig. 1.** Design strategy of compounds **10**.

The synthetic routes are shown in Schemes 1 and 2. Intermediates **1a–d** were prepared *via* a $S_NAr$ reaction of *o*-chloronitrobenzene derivatives and benzyl mercaptan sodium in refluxing ethanol. The intermediate **3** and **6** were synthesized through reactions with special region-selectivity reported by the literature.[14,15] **4** and **5** were obtained from **3** *via* Sandmeyer reaction in good yield. Intermediates **1a–d** were oxidized and chlorinated under the treatment of 1,3-Dichloro-5,5-dimethylhydantoin (DCDMH) and concentrate HCl in THF under 0 °C,[16,17] affording the corre-

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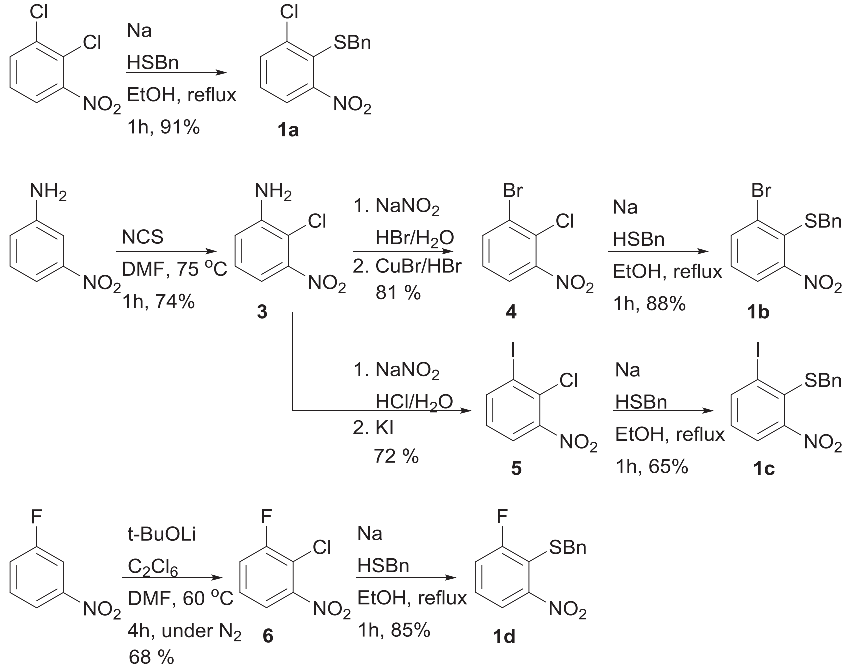
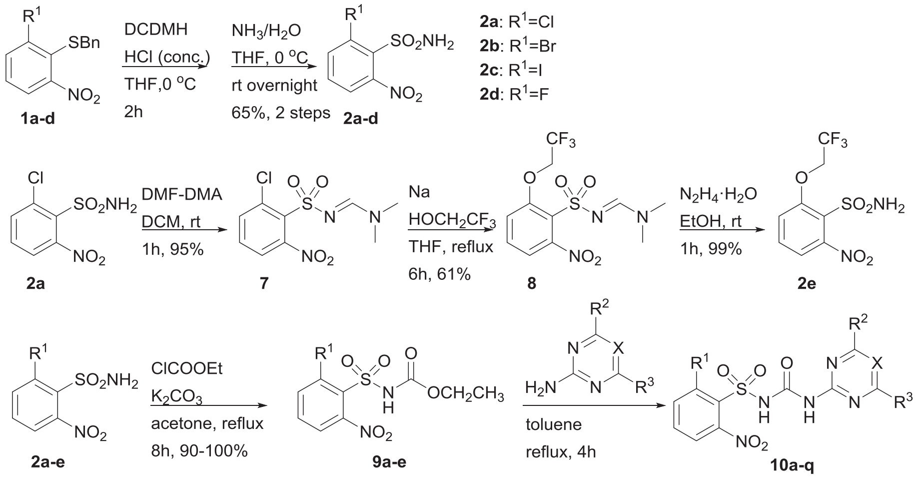


**Scheme 1.** Synthetic routes of intermediates **1a–d**.



**10a–q:**

**a** $R^1$=Cl,$R^2/R^3$=$CH_3/CH_3$,X=CH;
**b** $R^1$=Cl,$R^2/R^3$=$OCH_3/OCH_3$,X=CH;
**c** $R^1$=Cl,$R^2/R^3$=H/$CH_3$,X=CH;
**d** $R^1$=$OCH_2CF_3$,$R^2/R^3$=$CH_3/CH_3$,X=CH;
**e** $R^1$=Cl,$R^2/R^3$=$CH_3/OCH_3$,X=CH;
**f** $R^1$=Cl,$R^2/R^3$=Cl/$OCH_3$,X=CH;
**g** $R^1$=Cl,$R^2/R^3$=$CH_3/OCH_3$,X=N;
**h** $R^1$=F,$R^2/R^3$=$OCH_3/OCH_3$,X=CH;
**i** $R^1$=F,$R^2/R^3$=$CH_3/OCH_3$,X=CH;
**j** $R^1$=F,$R^2/R^3$=$CH_3$/H,X=CH;
**k** $R^1$=F,$R^2/R^3$=$CH_3/OCH_3$,X=N;
**l** $R^1$=I,$R^2/R^3$=$CH_3/OCH_3$,X=CH;
**m** $R^1$=I,$R^2/R^3$=$OCH_3/OCH_3$,X=CH;
**n** $R^1$=I,$R^2/R^3$=$CH_3$/H,X=CH;
**o** $R^1$=Br, $R^2/R^3$=$CH_3/OCH_3$,X=CH;
**p** $R^1$=Br, $R^2/R^3$=$OCH_3/OCH_3$,X=CH;
**q** $R^1$=Br, $R^2/R^3$=$CH_3/OCH_3$,X=N;

**Scheme 2.** Synthetic route of compounds **10a–q**.

sponding sulfonyl chlorides which were allowed to react immediately with excess ammonia hydroxide to give key intermediates **2a–d**. **2e** was prepared from **2a** through a substitution of Cl atom by 2,2,2-trifluoroethoxy group. In this reaction, the sulfonamide group of **2** was protected by *N*,*N*-Dimethylformamide dimethyl acetal (DMF-DMA) to avoid the failure caused by the side reaction of sulfonamide's deprotonation.[18] The protecting group was removed by stirring the intermediate **8** in excess hydrazine monohydrate in ethanol for an hour to attain **2e** in almost quantitative yield. The sulfonyl carbamates **9** were prepared in excellent yields by treating sulfonamides **2a–e** with ethyl chloroformate in the presence of fine powdered potassium carbonate in refluxing acetone. The reaction of sulfonyl carbamate and corresponding heterocyclic amine with continuous removal of the azeotrope of ethanol and toluene gives the desired products **10a–q**.

As shown in Table 1, derivatives **10a–q** were evaluated for their herbicidal activities based on the rape (*Brassica napus*) root test[19] at concentration of 0.1, 1 and 10 mg/L for an initial screening. Chlorsulfuron was selected as the positive control. Some compounds showed comparable herbicidal activity with chlorsulfuron under testing condition. The structure of the heterocycle moiety make a critical contribution to the herbicidal activities. The most